REMARKS

Claims 38-41 and 46-55 are pending in this application. Claims 49-55 are withdrawn from consideration by the Examiner as being directed to a non-elected invention. Claim 38 is amended herein for clarity and to more particularly define the invention. Support for this amendment is found throughout the specification and in the language of the original claims, as set forth below. It is believed that no new matter is added by this amendment and its entry and consideration are respectfully requested. In light of this amendment and the following remarks, applicants respectfully request examination of this application on the merits and allowance of the pending claims to issue.

I. Objection to specification- sequence compliance

The Office Action states that the application contains sequence disclosures that are not identified by the appropriate SEQ ID NOs from the Sequence Listing.

The specification is amended herein on pages 31-34, 38-39, 43 and 47 to incorporate the appropriate SEQ ID NOs from the Sequence Listing for sequences recited on these pages. Thus, this objection has been rendered moot and applicants respectfully request its withdrawal.

II. Drawings

The Office Action states that the drawings are objected to because they provide nucleic acid and amino acid sequences that are not identified by any SEQ ID NOs. The Office Action further states that there are drawings that span multiple pages, wherein the second and subsequent pages do not properly identify the drawing.

A set of replacement drawings is provided herewith, with any nucleic acid and amino acid sequences identified by the appropriate SEQ ID NOs from the Sequence Listing and also amended to identify the continuation of figures that span multiple pages. Thus, this objection has been rendered moot and applications respectfully request its withdrawal.

III. Objection to the specification

The Office Action states that the specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code and that applicant is required to delete these.

The specification is amended herein on pages 27-29 and 45 to remove any embedded hyperlinks. Thus, this objection has been rendered moot and applicants respectfully request its withdrawal.

IV. Rejection under 35 U.S.C. § 112, second paragraph

The Office Action states that claims 38-41 and 46-48 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite on the basis that the claims recite only a single active step and that there is no nexus between the purpose of the method as stated in the preamble and the single required step.

Claim 38 as presented herein recites a method of identifying a human subject as having susceptibility to schizophrenia and/or affective psychosis, wherein the method comprises determining if the *GRIK4* gene in the human subject has been disrupted by a mutation or chromosomal rearrangement, wherein a determination that the GRIK4 gene in the subject has been disrupted by a mutation or chromosomal rearrangement identifies the subject as having susceptibility to schizophrenia and/or affective psychosis. As such, claim 38 is now clear regarding how the stated purpose, that of identifying a human subject as having susceptibility to schizophrenia and/or affective psychosis, is accomplished in the recited method step and in establishing a nexus between the stated purpose of the claimed method and the recited step. The present invention is based on the applicants' discovery of a correlation between the presence of a mutation or chromosomal rearrangement in the GRIK4 gene of a subject and schizophrenia in that subject and the claimed invention sets forth the practical application of that discovery; i.e., the analysis of nucleic acid of any subject for the presence of disruption of the GRIK4 gene by a mutation or

chromosomal rearrangement in the subject on the basis that the presence of such a mutation or chromosomal rearrangement of the GRIK4 gene identifies that subject as having susceptibility to schizophrenia and/or affective psychosis. Thus, applicants believe the invention as claimed herein to be of sufficient clarity to allow one of ordinary skill in the art to recognize what the applicants regard as the invention, thereby overcoming this rejection of claim 38 and claims39-41 and 46-48 dependent therefrom and applicants respectfully request its withdrawal.

V. Rejection under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 38-41 and 46-48 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Examiner sets forth an analysis of the claimed invention based on the factors set forth in *In re Wands* and cites various references to support his assertion that the invention as claimed lacks enablement. These factors are 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented; 3) direction provided by the specification and working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

Applicants respectfully traverse this rejection and provide their own analysis of the claimed invention pursuant to the factors set forth in *In re Wands*, demonstrating that the present invention is indeed enabled.

As an initial point, applicants respectfully point out that it is well established that the test for enablement is whether one skilled in the art could reproduce the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The key word is "undue," not "experimentation," and "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804, 807 (CCPA 1982)). In *Wands*, claims to antibodies that required a screening procedure to isolate the desired hybridoma cells from enormous numbers of

other cells present in the reaction mixture were held to not require experimentation that was "undue." *Id.*, 8 USPQ2d at 1406. The amount of effort required to make the antibodies was "not excessive." *Id.*, 8 USPQ2d at 1407. Thus, the test of enablement under 35 USC §112, first paragraph, is not whether any experimentation is necessary but rather is whether one skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *See,* MPEP 2164.01.

Nature of the invention and breadth of the claims

In an analysis of the factors of *In re Wands* regarding the nature of the invention and the breadth of the claims, applicants point out that the invention as presented herein is directed to a method of identifying a human subject as having susceptibility to schizophrenia and/or affective psychosis, wherein the method comprises determining if the *GRIK4* gene in the human subject has been disrupted by a mutation or chromosomal rearrangement, wherein a determination that the *GRIK4* gene in the subject has been disrupted by a mutation or chromosomal rearrangement identifies the subject as having susceptibility to schizophrenia and/or affective psychosis (claim 38). This method can be carried out by detecting a relative level of mRNA expressed by the *GRIK4* gene (claim 39) by an immunological technique (claims 40-41) or by FISH (claims 46-48). Thus, the invention as claimed herein is clear and well defined in its scope.

Direction provided by the specification and working examples

As noted above, the claimed invention is the practical application of applicants' discovery of a mutation or chromosomal rearrangement in the GRIK4 gene of a subject with schizophrenia. That this discovery allows those of ordinary skill in the art to identify any human subject as having susceptibility to schizophrenia and/or affective psychosis by detecting a mutation or chromosomal rearrangement in the GRIK4 gene of such a subject is explained by co-inventor, Dr. Benjamin Pickard, as set forth in the enclosed Declaration under 37 C.F.R. § 1.132 and in the enclosed publication by the inventors (Pickard et al. "Cytogenetic and genetic evidence supports a role for the kainite-type glutamate receptor gene, *GRIK4*, in schizophrenia and bipolar disorder" *Molecular Psychiatry*, pp. 1-11 (2006)).

The specification provides working examples with actual reduction to practice of the claimed invention and provides more than ample guidance for one of ordinary skill to identify a human subject as having susceptibility to schizophrenia and/or affective psychosis as claimed herein without undue experimentation. In particular, the ordinary artisan could and would use the teachings of the specification of a correlation between a mutation or chromosomal rearrangement of the GRIK4 gene and schizophrenia, coupled with knowledge in the art at the time this invention was made, to carry out further correlation studies and identify human subjects susceptible to schizophrenia and/or affective psychosis with nothing more than routine experimentation. Thus, similar to the holding of the court in *In re Wands*, "...all of the methods needed to practice the invention were well known." *Id.*, 8 USPQ2d at 1406.

For at least the reasons provided above, applicants have demonstrated that these *Wands* factors regarding the amount of guidance, available not only in the present specification but also in the art, as well as the presence of working examples of the claimed invention, weigh in the applicants' favor.

State of the art, level of skill in the art, and level of unpredictability

To address these factors, the Office Action states that while "...the level of skill in the art with regard to determining if a particular gene sequence has an alteration is high, the level of unpredictability in correlating any detected nucleic acid sequence mutation with a particular diagnosis, such as schizophrenia or any affective psychosis, is even higher." The Examiner continues on with this analysis by noting that the pending claims encompass non-human organisms and that there is unpredictability in extrapolating results regarding the asserted association of an allele with a phenotype in humans to any other organism, citing Juppner. The Examiner also cites Orntoft et al. and Chan as alleged evidence of unpredictability as to whether the detection of GRIK4 gene product levels would be indicative of the particular disruption that is taught in the specification. Furthermore, the Examiner cites Li et al. and Shibata et al. as allegedly relevant in view of the breadth of the mutations encompassed by the claims and cites Lucentini, Baysal et al. and Hacker et al. as alleged evidence of the general unpredictability of gene association studies.

In response to the Examiner's arguments regarding the general unpredictability in associating any genotype with a phenotype, the applicants point out that although the biological sciences have been generally categorized as "unpredictable," the courts have long and repeatedly emphasized that the issue is not predictability *per se*, but the type of work and experimentation acceptable in the particular field, or fields, of the invention. For example, in *In re Angstadt,* the Court of Customs and Patent Appeals cautioned that:

> "If [our prior decision stands] for the proposition that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction,* whether the claimed product will be obtained,.... then *all* 'experimentation' is 'undue', since the term 'experimentation' implies that the success of the particular activity is *uncertain.* Such a proposition is contrary to the basic policy of the patent act...."

In re Angstadt, 537 F. 2d 498, 503, 190 USPQ 214, 218-219 (CCPA 1976).

The court in *Angstadt* went on to emphasize that "...the key word is 'undue,' not 'experimentation'." *Id* at 504, 190 USPQ at 219. Thus, it is clear that even in an "unpredictable" art, an invention can be enabled, provided that the amount of experimentation required to carry out the invention is not undue.

The Office Action further comments that the specification teaches a single chromosomal rearrangement and that there is no analysis of the functional consequences of the GRIK4 rearrangement. Applicants respectfully point out that one of ordinary skill in the art would recognize the functional consequences of the described GRIK4 rearrangement, as well as any other GRIK4 mutation or rearrangement, as such mutations and rearrangements pertain to susceptibility to schizophrenia and/or affective psychosis, as explained in the enclosed Declaration. Furthermore, such mutations or rearrangements could be detected at the level of GRIK4 mRNA as well as at the level of GRIK4 gene product, as also explained in Dr. Pickard's Declaration.

The applicants also respectfully point out that there is no legal requirement for enablement that a particular degree of statistical significance be demonstrated or indeed that any statistical significance be demonstrated to meet the enablement requirement for patentability. Applicants also note that the question of the relevance of statistical significance was considered by the Court of Customs and Patent Appeals in *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), in interpreting the utility requirement under 35 U.S.C. § 101. In *Nelson*, the court explicitly rejected the argument that "confirmation by statistically significant means" was required to meet the utility requirement. *Id.* at 883. The court, instead, stated that the pharmacological activity at issue in that case need only be "reasonably indicative of the desired response." *Id.* at 884. Applicants respectfully submit that although the court in *Nelson* was addressing a utility rejection, that a very similar argument can be applied to address the present enablement rejection, namely that the claimed association between susceptibility in a subject and the presence of a mutation or chromosomal rearrangement of the GRIK4 gene of that subject would clearly be recognized by one of skill in the art as a valid and real association.

Thus, for at least the reasons set forth above, it is the applicants' view that these factors weigh in favor of enablement of the claimed invention.

Finally, the Office Action addresses the *Wands* factor regarding the quantity of experimentation necessary to carry out the claimed invention by stating that "...an undue amount of experimentation would be required to make and use the invention in the full scope of the claims."

In reply, the applicants respectfully remind the Examiner that in an analysis of whether the claimed invention is enabled, the quantity of experimentation needed to be performed by one of skill in the art is only one factor to be considered and should be considered in the appropriate context of what would be considered undue, even if extensive. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient guidance." *In re Colianni*, 561 F.2d 220, 224,

195 USPQ 150, 152 (CCPA 1977). Furthermore, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737 (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 218 (CCPA 1976).

In the present invention, as the applicants have noted above, all of the methods needed to carry out the claimed invention were known at the time of this invention and the level of skill of those in this art would be recognized to be quite high. Furthermore, not only does the specification as filed provide more than ample guidance to carry out the methods of this invention, the specification includes an actual reduction to practice of the claimed invention. The methods provided in the present specification as well as those available in the art at the time of this invention are straightforward and routine and there is no evidence to support a statement that carrying out these methods would require experimentation that would be "undue."

In conclusion, applicants respectfully point out that in a determination of whether the enablement requirement is satisfied, the Examiner must consider all the evidence related to each of the above factors and any conclusion of non-enablement must be based on the evidence as a whole. *In re Wands*, at 737, 740, 8 USPQ2d, at 1404, 1407. For the present invention, when the evidence as a whole is considered, it is apparent that the methods of the claimed invention do not require undue experimentation, and thus claims 38-41 and 46-48 satisfy the requirement for enablement. Applicants therefore respectfully request that this rejection be withdrawn.

VI. Rejection under 35 U.S.C. § 102(b)

A. The Office Action states that claim 38 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Gurling et al. Specifically, the Action states that Gurling et al. teaches an analysis of human chromosome 11, including an analysis of the microsatellite marker D11S925 and that because this marker is contained in the GRIK4 gene (as disclosed in the specification on page 37,

line 35 to page 38, line 1), the analysis of Gurling et al. is determining if the GRIK4 gene in an individual has been disrupted by a mutation.

Applicants note that the Examiner is basing this rejection on a reading of the claims pursuant to his interpretation of MPEP § 2111.02 as supporting the position that "...the preambles of the claims and the recitations of the intended use of the claimed methods are not given weight when comparing the required limitations of the claimed methods to those taught by the prior art." The Office Action further provides the following as a direct quote from MPEP § 2111.02:

> A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness, but instead, the process steps or structural limitations are able to stand alone.

The Examiner continues on with a citation to *Pitney Bowes, Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, in which he alleges that "...the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give 'life, meaning and vitality' to the claim, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation."

Applicants have reviewed the most recent version of MPEP § 2111.02 available on the USPTO website and do not find the quoted passage above nor do they agree with the Examiner's interpretation of the court's holding in *Pitney Bowes*. Specifically, what is stated about the *Pitney Bowes* case in MPEP § 2111.02 is the following: "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." In the present application, the recitation in the preamble in claim 38 of "identifying a human subject having susceptibility to schizophrenia and/or affective psychosis" is indeed necessary to give life, meaning and vitality to the claim, thereby reciting an essential limitation of the claim and without which the body of the claim is incomplete.

Thus, claim 38 as presented herein must be properly read as reciting a method of identifying a human subject as having susceptibility to schizophrenia and/or affective psychosis, wherein the method comprises determining if the *GRIK4* gene in the human subject has been disrupted by a mutation or chromosomal rearrangement, wherein a determination that the GRIK4 gene in the subject has been disrupted by a mutation or chromosomal rearrangement identifies the subject as having susceptibility to schizophrenia and/or affective psychosis. Gurling et al. provides no teaching of identifying a human subject as having susceptibility to schizophrenia and/or affective psychosis by determining if the *GRIK4* gene in the human subject has been disrupted by a mutation or chromosomal rearrangement and it is well established in the case law that anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention. *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). It is clear that Gurling et al. fails to anticipate claim 38 because Gurling et al. fails to teach each and every limitation of the method set forth in this claim.

B. The Office Action states that claims 38 and 46-48 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Szpirer et al. Specifically, the Action states that Szpirer et al. teaches the chromosomal localization of the GRIK4 gene in humans and also teaches FISH analysis and the use of labeled oligonucleotides.

For the same reasons set forth above regarding Gurling et al., the Szpirer et al. reference fails to anticipate claims 38 or 46-48 because Szpirer et al., like Gurling et al., does not provide any teachings regarding identifying a subject as having susceptibility to schizophrenia and/or affective psychosis by determining if the *GRIK4* gene in the human subject has been disrupted by a mutation or chromosomal rearrangement. Therefore, Szpirer et al. fails to teach each and every limitation of the methods set forth in these claims.

Thus, for at least the reasons set forth above, applicants believe these anticipation rejections have been overcome and their withdrawal is respectfully requested.

The Examiner is encouraged to contact the undersigned directly if such contact will expedite the examination and allowance of the pending claims.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $525.00 as fee for a three-month extension of time for a small entity, which status is asserted herein for this application pursuant to 37 C.F.R. § 1.27(c)(3). This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4) to the U.S. Patent and Trademark Office on September 17, 2008.

Claire Wimberly